UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: November 10, 2020

Subject: **Benzovindiflupyr**. Section 3 Registration for the New Use of Benzovindiflupyr on Lowbush Blueberries and Ginseng. Abbreviated Summary of Analytical Chemistry and Residue Data.

PC Code: 122305
Decision No.: 557710
Petition No.: 9E8806
Risk Assessment Type: NA
TXR No.: NA
MRID No.: 50803801 and 50803802

DP Barcode: D459762
Registration No.: 100-1471, 100-1476, 100-1479, 100-1480
Regulatory Action: R170 Additional Food Use
Case No.: NA
CAS No.: 1072957-71-1
40 CFR: §180.686

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1.0 Executive Summary

Benzovindiflupyr (*N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide) is a pyrazole carboxamide and a member of the SDHI (Succinate Dehydrogenase Inhibitors) class of fungicides. This active ingredient (ai) is currently registered for use on numerous crops including, cereals (wheat, triticale, barley, rye, and oat); blueberries (non-bearing); sugarcane; bulb onions, and green onions; corn (field, pop, and sweet); cottonseed (subgroup 20C); cucurbit vegetables (group 9); fruiting vegetables (crop group 8-10); small fruit vines climbing, except fuzzy kiwifruit (subgroup 13-07F); legume vegetables (subgroup 6C); peanuts; pome fruit (crop group 11-10); rapeseed (subgroup 20A); and tuberous and corm vegetables (subgroup 1C) as well as use on turf, ornamentals, and grasses grown for seed.

The Interregional Research Project #4 (IR-4) has submitted a petition to propose the use of benzovindiflupyr on ginseng and lowbush blueberry for EPA Reg. Nos 100-1471, 100-1476, and 100-1480. In support of this action, IR-4 has submitted MRID Nos. 50803801 and 50803802 detailing the magnitude of the residue (MOR) field trial studies.

Conclusions: HED concludes that an adequate number of MOR field trial studies were conducted with appropriate geographic representation. All samples were analyzed using a validated analytical method and were supported by sufficient storage stabilty data.

Tolerances are currently established under 40 CFR §180.686 for residues of benzovindiflupyr. HED recommends that new tolerances for blueberry, lowbush and ginseng be added to 40 CFR §180.686(a).

> (a) General. Tolerances are established for residues of the fungicide benzovindiflupyr, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only benzovindiflupyr (N-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide) in or on the commodity.

Table 1 Tolerance Summary for Benzovindiflupyr.

Commodity	Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Blueberry, lowbush	2	2	
Ginseng	0.3	0.3	

The proposed uses are not expected to increase livestock dietary burden as blueberry and ginseng are not considered a significant feed item. The proposed uses are expected to result in changes to the estimated dietary exposures to benzovindiflupyr residues.

A human health risk assessment is forthcoming.

Detailed Considerations

Residues of Concern Summary and Rationale

ROCKS Decision Memo D416202, I. Negron-Encarnacion, February 3, 2014

The residue chemistry database for benzovindiflupyr is complete and the nature of the residue is adequately understood. Data from plant and livestock metabolism studies, as well as toxicological and environmental fate data were considered by the Residues of Concern Knowledgebase Subcommittee (ROCKS) (I. Negron-Encarnacion, D416202, 03 February 2014). The residues of concern (ROCs) for risk assessment and tolerance expression of benzovindiflupyr in/on plants, livestock, and drinking water are summarized in Table 2 below.

Table 2. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression. [1]

Matrix		Residues Included in Risk Assessment	Residues Included in Tolerance Expression
Plants	Primary Crop	Benzovindiflupyr and SYN546039	Benzovindiflupyr
	Rotational Crop	Benzovindiflupyr and SYN546039	Benzovindiflupyr
Livestock	Ruminant	Benzovindiflupyr and SYN546039	Benzovindiflupyr
	Poultry	Benzovindiflupyr and SYN546039	Benzovindiflupyr
Drinking Water		Benzovindiflupyr	Not Applicable

[1] Refer to Appendix 1 of D417210 for the names and/or chemical structures of the metabolites/degradates.

Data Collection Methods

Samples of lowbush blueberry and ginseng were analyzed for residues of benzovindiflupyr and metabolite SYN546039 (including conjugates) by LC/MS/MS using Syngenta Analytical Method GRM042.03A, entitled "SYN545192 – Analytical Method GRM042.03A for the Determination of SYN545192 and its Metabolite SYN546039 in Crops," with modifications. This method was previously deemed acceptable (P. Savoia, 01/15/2015, D417210).

Acceptable method validation and concurrent recoveries were obtained from samples lowbush blueberries and ginseng fortified with benzovindiflupyr and SYN546039, at 0.01, 0.02, 0.1, and 2.0 ppm for blueberries and at 0.01, 0.1, and 1.0 ppm for ginseng. The limit of quantitation (LOQ) was 0.01 ppm for both commodities. The fortification levels adequately represent the measured residues from the field trial studies.

Submittal of Analytical Reference Standards (860.1650)

The National Pesticides Standards Repository has supplies of the benzovindiflupyr analytical reference standard with the indicated expiration date (e-mail from G. Verdin, 02/19/2020):

Standard	CAS#	Expiration Date
Benzovindiflupyr	1072957-71-1	06/30/2023

Storage Stability (860.1380)

Freezer storage stability data were previously reviewed and results indicate that residues of benzovindiflupyr were stable when stored frozen at ≤ 0°F (≤ -18 C) in crops from all representative OECD commodity categories (*i.e.* spinach (high water content), orange fruit (high acid content), soybean seed (high oil content), dried broad bean (high protein content) and potato tuber and wheat grain (high starch content)) for at least 24 months (730 – 734 days) (P. Savoia, 01/15/2015, D417210). Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

Table 3 Summary of Storage Conditions of Benzovindiflupyr

Matrix (RAC)	Storage Temperature (°F)/[°C]	Actual Storage Duration (days)[1]	Interval of Demonstrated Storage Stability (days/months)
Blueberries	≤ 0°F [≤ -18°C]	227	Freezer storage stability data were previously reviewed and results demonstrated that residues of benzovindiflupyr and metabolite SYN546039 were stable when stored frozen for at least 24 months (730-734 days) in crops from all representative OECD commodity categories (high water, high acid, high oil, high starch and high protein) (D417210).
Dried ginseng roots	≤ 0°F [≤ -18°C]	460	

5.3.1 Crop Field Trials (860.1500)

50803801.der
50803802.der

For this action IR-4 has submitted petition PP#9E8806 which request to establish tolerances for the active ingredient benzovindiflupyr on lowbush blueberries and ginseng. Review of this data was conducted as a joint review with PMRA. Sufficient number of trials were conducted in geographically appropriate regions to support the establishment of tolerances (Table 4).

Table 4. Trial Numbers and Geographical Locations.

Crop	No. Trials	NAFTA Growing Zone												Total
		1A	2	3	4	5	6	7	8	9	10	11	12	
Lowbush blueberries	Sub.	5												5[1]
	Req.													5
Ginseng	Sub.					4								4
	Req.													3

[1] Adequate for lowbush blueberry registration per ChemSAC decision (12/29/2018).

For these uses, supervised crop field trials with benzovindiflupyr were conducted in the U.S. employing the maximum labeled use pattern (0.136 lb ai/year lowbush blueberry and 0.272 lb ai/year ginseng) and were harvested at preharvest intervals (PHIs) ranging from 1 day for lowbush blueberries and 15 days for ginseng. All matrices were analyzed for residues of benzovindiflupyr and the metabolite SYN546039 according to the data collection methods described previously. Table 5 provides a summary of the field trial results for determining magnitude of the residues in lowbush blueberries and ginseng.

Table 5 Summary of Residues from Field Trials with Benzovindiflupyr.											
Crop Matrix	Analyte	Applic. Rate (lb ai/acre)	PHI (days)	n*	Residues (ppm)						
					Max.†	Min.†	HAFT*	LAFT*	Median*	Mean*	SD*
Blueberry, lowbush Proposed Use = 0.136 lb ai/acre total application rate, 1-day PHI.											
Lowbush Blueberries	Benzovindiflupyr	0.132-0.137	1	5	0.981	0.475	0.866	0.655	0.640	0.156	0.981
Ginseng Proposed Use = 0.272 lb ai/acre total application rate, 15-day PHI.											
Dried Ginseng Roots	Benzovindiflupyr	0.268-0.278	15	4	0.161	0.0336	0.145	0.0755	0.0824	0.0487	0.161
	SYN546039[1]				<0.01	<0.01	<0.01	<0.01	<0.01	-	<0.01
	Combined Residues				<0.171	<0.0436	<0.155	0.0855	0.0924	0.0487	<0.171

[1] Residues of metabolite SYN5460139 were not expressed as parent equivalents since these were below LOQ (<0.01 ppm).
† Values based on total number of samples.
* Values based on per-trial averages. LAFT = Lowest Average Field Trial, HAFT = Highest Average Field Trial, SD = Standard Deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values < LOQ are assumed to be at the LOQ (0.01 ppm).

Conclusions. The submitted residue data are adequate to satisfy all data requirements for determining the magnitude of the residue for lowbush blueberry and ginseng. An adequate number of trials were performed and did represent good agricultural practices (GAP) of that region. Residue decline studies were conducted in ginseng with PHIs ranging from 0-21 days and showed residues decreased between 0-8 days and increased at a PHI of 21 days.

Tolerance Derivation

The recommended tolerances for the residues of benzovindiflupyr in/on lowbush blueberries and ginseng were obtained using the OECD MRL calculation procedures. The residue data and calculation procedure outs are included below (Appendix A). Based on these calculations new tolerances are recommended for lowbush blueberries and ginseng.

There are currently no maximum residue levels set by either Canada or Codex (See Appendix B). However, this petition was a joint review with PMRA and tolerances will be harmonized for lowbush blueberry and ginseng.

Food Residue Profile

Adequate residue chemistry data have been provided to support the registration of benzovindiflupyr on lowbush blueberry and ginseng. Data analyses used validated analytical methods and are supported by adequate storage stability data.

The metabolism of benzovindiflupyr was investigated in three different plants, i.e., tomato, soybean, and wheat. Parent benzovindiflupyr was identified as the major residue in metabolism studies and in multiple crop field trials. In the available crop field trials, benzovindiflupyr was found in most of the food and feed crops at quantifiable levels but occurred more often in the foliage and forage and was generally below the LOQ (0.01 ppm) in grain and seed. The primary biotransformation product observed in both the metabolism studies and crop field trials is hydroxylated benzovindiflupyr (SYN546039). In crop field trials, this metabolite was generally found at levels near the LOQ (0.01 ppm) except in the foliage and forage portions of plants

where the residues were typically greater. Detectable residues of benzovindiflupyr are not expected in rotational crops following a 180-day plant back interval. Data demonstrate that residues of benzovindiflupyr and the SYN546039 metabolite are stable in raw agricultural crops and processed commodities when stored at or below -10°C for at least 22-24 months.

Benzovindiflupyr plus SYN546039 residues were found to concentrate in the processed commodities of apple wet pomace, aspirated grain fractions (AGF), peanut oil, potato processed waste, raisin, soybean hulls, dried tomatoes, and sugar beet dried pulp. Benzovindiflupyr residues did not concentrate in refined sugar and molasses.

Secondary residues of benzovindiflupyr may occur in milk, beef fat, kidney, and liver. The physiochemical properties of benzovindiflupyr indicate it is moderately lipophilic with a tendency to dissolve in fats, oils, lipids, and non-polar solvents. This is consistent with the livestock metabolism and feeding study data which show benzovindiflupyr residues concentrate in fat and milk cream. For poultry and swine, there is no expected secondary transfer of benzovindiflupyr. For the requested new use on lowbush blueberries and ginseng the new uses will not increase cattle dietary burden; therefore, no revised tolerances on livestock commodities are required.

Appendix A. OECD MRL Calculation Procedure Inputs/Outputs

Compound	Benzovindiflupyr	Benzovindiflupyr
Crop	Lowbush blueberries	Ginseng
Region / Country	Canada	USA
GAP	0.132-0.137 lb ai/A; PHI 1d	0.268-0.278 lb ai/A; PHI 15-21 d
Total number of data (n)	5	4
Percentage of censored data	0%	0%
Number of non-censored data	5	4
Lowest residue	0.475	0.034
Highest residue	0.866	0.145
Median residue	0.655	0.081
Mean	0.640	0.085
Standard deviation (SD)	0.156	0.047
Correction factor for censoring (CF)	1.000	1.000
Proposed MRL estimate		
- Highest residue	0.866	0.145
- Mean + 4 SD	1.265	0.273
- CF x 3 Mean	1.919	0.256
Unrounded MRL	1.919	0.273
Rounded MRL	2	0.3
	High uncertainty of MRL estimate due to small dataset.	High uncertainty of MRL estimate due to small dataset.

Residues (mg/kg)		Residues (mg/kg)	
0.655		0.0945	
0.691		0.0336	
0.475		0.1450	
0.511		0.0677	
0.866			

Appendix B. International Residue Limits

Summary of U.S. and International Tolerances and Maximum Residue Limits			
Residue Definition:			
U.S. - 40 CFR 180.686: Plant: Benzovindiflupyr (N-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide) Livestock: Benzovindiflupyr (N-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide)			
Canada - Benzovindiflupyr			
Codex - Benzovindiflupyr			
Commodity	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*		
	U.S.	Canada	Codex
Barley, grain	1.5	1.5	1
Barley, hay	15.0		
Barley, straw	15.0		
*Blueberry, lowbush**	2	2	
Bluegrass, forage	0.15		
Bluegrass, hay	7.0		
Bluegrass, straw	6.0		
Bromegrass, forage	0.15		
Bromegrass, hay	7.0		
Bromegrass, straw	6.0		
Cattle, fat	0.02	0.02	0.03
Cattle, liver	**0.06**	**0.04**	**0.1**
Cattle, meat	0.01	0.01	0.03
Cattle, meat byproducts, except liver	0.01	0.01	0.1
Coffee, green bean	0.09	0.09	0.15
Corn, field, forage	3.0		
Corn, field, grain	0.02	0.02	
Corn, field, stover	15.0		
Corn, pop, grain	0.02	0.02	
Corn, pop, stover	15.0		
Corn, sweet, forage	4.0		
Corn, sweet, kernel plus cob with husks removed	0.01	0.01	0.01
Corn, sweet, stover	5.0		
Cottonseed, subgroup 20C	0.15	0.15	
Cotton, gin byproducts	3.0		
Fescue, forage	0.15		
Fescue, hay	7.0		
Fescue, straw	6.0		
Fruit, pome, group 11-10	0.20	0.2	0.2
Fruit, small vin climbing, except fuzzy kiwifruit, subgroup 13-07F	1.0	1	1
*Ginseng**	0.3	0.3	
Goat, fat	0.02	0.02	0.03
Goat, liver	**0.06**	**0.04**	**0.1**
Goat, meat	0.01	0.01	0.03
Goat, meat byproducts, expect liver	0.01	0.01	0.1
Grain, aspirated fractions	15.0		
Grape, raisin	3.0	3	3
Horse, fat	0.02	0.02	0.03
Horse, liver	**0.06**	**0.04**	**0.1**
Horse, meat	0.01	0.01	0.03

Summary of U.S. and International Tolerances and Maximum Residue Limits			
Residue Definition:			
U.S. - 40 CFR 180.686: Plant: Benzovindiflupyr (N-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide) Livestock: Benzovindiflupyr (N-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide)			
Canada - Benzovindiflupyr			
Codex - Benzovindiflupyr			
Horse, meat byproducts, except liver	0.01	0.01	0.1
Milk	0.01	0.01	0.01
Milk, fat	0.02	0.02	
Oat, grain	1.5	1.5	1
Oat, hay	15.0		
Oat, straw	15.0		
Onion, bulb, subgroup 3-07A	0.02	0.02	
Onion, green, subgroup 3-07B	0.40	0.4	
Orchardgrass, forage	0.15		
Orchardgrass, hay	7.0		
Orchardgrass, straw	6.0		
Pea and bean, dried shelled, except soybean, subgroup 6C	0.20	0.2	0.15
Pea, field, hay	7.0		
Pea, field vine	1.5		
Peanut	0.01	0.01	
Peanut, hay	15.0		
Potato, processed potato waste	0.10		
Rapeseed, subgroup 20A	0.15	0.15	0.2
Rye, grain	0.1	0.1	0.1
Rye, hay	15.0		
Rye, straw	15.0		
Ryegrass, forage	0.15		
Ryegrass, hay	7.0		
Ryegrass, straw	6.0		
Sheep, fat	0.02	0.02	0.03
Sheep, liver	**0.06**	**0.04**	**0.1**
Sheep, meat	0.01	0.01	0.03
Sheep, meat byproducts, except liver	0.01	0.01	0.1
Soybean, forage	15.0		
Soybean, hay	50.0		
Soybean, hulls	0.20		
Soybean, seed	0.07	0.07	0.08
Sugarcane, cane	0.30	0.3	0.04
Tomato, dried	4.0	4	
Vegetable cucurbit, group 9	0.30	0.3	0.2
Vegetable, fruiting, group 8-10	1.5	1.5	0.9
Vegetable, tuberous and corm, subgroup 1C	0.02	0.02	0.02
Wheat, forage	4.0		
Wheat, grain	0.10	0.1	0.1
Wheat, hay	15.0		
Wheat, straw	15.0		15
Completed: D. Nadrchal; 03/30/2020 using Global MRL			

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Blueberries (lowbush and highbush)

Document ID:	MRID No. 50803801 PMRA No. 3040359
Report:	Ahn, B. (2019) "Benzovindilflupyr: Magnitude of the Residue on Blueberries, Lowbush and Highbush", Study Number: AAFC16-039R. Unpublished study prepared by Pest Management Centre, Agriculture and Agri-Food Canada, Ottawa, ON, Canada, 223p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996) PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements OECD Guideline 509 Crop Field Trial (September 2009)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable.
Evaluator:	Natalie Gaudreau, MUAS, HED, PMRA David Nadrchal, EPA

David Nadrchal

EXECUTIVE SUMMARY

Nine field trials for benzovindiflupyr on blueberries (lowbush and highbush) were conducted in Canada during the 2016 growing season. Five field trials on lowbush blueberries were conducted in North American Free Trade Agreement (NAFTA) Growing Region 1A (5 trials in NS), and 4 field trials on highbush blueberries were conducted in Growing Regions 5/5B (1 trial in ON and 1 trial in QC) and 12 (1 trial in BC).

At each trial location, benzovindiflupyr formulated as Aprovia Fungicide (emulsifiable concentrate containing 10.3% w/w benzovindiflupyr) was applied twice as a foliar broadcast application to lowbush blueberries and as a foliar directed application to highbush blueberries. At 7 trial sites, lowbush and highbush blueberries were treated at a rate of 0.066 to 0.070 lb a.i./A (74 to 79 g a.i./ha) with retreatment intervals (RTIs) of 9 to 10 days for a total seasonal rate of 0.132 to 0.139 lb a.i./A (148 to 156 g a.i./ha). In the remaining two highbush blueberry trials, benzovindiflupyr was applied at a rate of 0.202 to 0.206 lb a.i./A (226 to 231 g a.i./ha) with RTIs of 10 days for a total seasonal rate of 0.407 to 0.411 lb a.i./A (461 to 456 g a.i./ha). An adjuvant, Agral 90, was added to the spray mixture for all applications at a rate of 0.2% v/v. Blueberries (lowbush and highbush) were harvested at a preharvest interval (PHI) of 1 day. In one highbush blueberry trial, samples were collected at different time intervals (PHIs of 5, 7, 11

and 14 days) to monitor residue decline.

All samples were maintained frozen at the testing facility, during shipping to the laboratory, and were stored frozen until analysis. The maximum storage interval for samples between harvest and extraction was 227 days. Samples were analyzed within 1 day of extraction. Residues of benzovindiflupyr have been shown to be stable in crops from all representative OECD commodity categories (*i.e.* spinach (high water content), orange fruit (high acid content), soybean seed (high oil content), dried broad bean (high protein content) and potato tuber and wheat grain (high starch content)) for up to 730-734 days under frozen conditions. Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

Samples in the current study were analyzed using a working method based on the reference Method GRM042.03A, a LC-MS/MS method to determine residues of benzovindiflupyr. Acceptable method validation and concurrent recoveries were reported for blueberry samples at fortification levels of 0.01, 0.02, 0.1 and/or 2.0 mg/kg (ppm), thus validating the method. The limit of quantitation (LOQ) was 0.01 ppm for blueberries.

Individual sample (and per-trial average) residues of benzovindiflupyr in **lowbush blueberries** ranged from 0.436 ppm to 0.981 ppm (0.475 ppm to 0.866 ppm) following two foliar broadcast applications at a total seasonal rates of 0.132 to 0.137 lb a.i./A (148 to 153 g a.i./ha) and harvested at a PHI of 1 day.

Individual sample (and per-trial average) residues of benzovindiflupyr in **highbush blueberries** ranged from 0.516 ppm to 1.051 ppm (0.537 ppm to 0.861 ppm) following two foliar directed applications at a total seasonal rates of 0.140 lb a.i./A (156 g a.i./ha) and harvested at a PHI of 1 day. In highbush blueberries treated with two foliar directed application at a total seasonal rates of 0.407 to 0.411 lb a.i./A (456 to 461 g a.i./ha) and harvested at a PHI of 1 day, individual sample (and per-trial average) residues of benzovindiflupyr ranged from 0.337 ppm to 0.551 ppm (0.360 ppm to 0.514 ppm).

In the residue decline trial on highbush blueberries, residues of benzovindiflupyr decreased from PHIs of 0 to 11 days and slightly increased from PHIs of 11 to 14 days.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for Benzovinflupyr.	
Common name	Benzovinflupyr
Identity	*N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide
CAS no.	1072957-71-1
Company experimental name	SYN545192

B. Study Design

1. Test Procedure

A total of 9 residue trials in/on blueberries (lowbush and highbush) were conducted with an emulsifiable concentration formulation during the 2016 growing season (Table B.7.6.1.1-2).

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.

Crop	Region														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Lowbush blueberries	5	-	-	-	-	-	-	-	-	-	-	-	-	-	5
Highbush blueberries	-	-	-	-	3	-	-	-	-	-	-	1	-	-	4

All trials, except for those listed in the table below, were separated by ≥ 20 miles (≥ 32 km) and are therefore considered independent (568_Criteria for Independence of Trials, November 2014). The trials separated by < 20 miles (< 32 km) have been assessed for independence as detailed in the table below. HED has determined that there are sufficient differences between the trials that they may be considered separate.

Independent Trial Determination[1]		
Trial Nos.	Differences	Decision
157 and 158	Location: L'Acadie, QC Variety: Patriot (Trial no. 157) and Norland (Trial no. 158) Timing: 1st applications were made the same day. Spray mixture: an independent spray mixture was prepared for each trial site[2].	Separate due to different varieties and an independent spray mixture was used.

[1] All assessments are based on the replicate trial guidance presented in memorandum Criteria for Independence of Crop Field Trials, November 2014.

[2] The sponsor confirmed that a different spray mixture was used at each trial site (PMRA #3110912).

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3.

Table B.7.6.1.1-3. Study Use Pattern.

Location: City, Province; Year (Trial ID)	End-use Product/ Formulation (% ai)	Method of Application/ Timing of Application	Volume (gal/A) [L/ha]	Rate per Application (lb a.i./A) [g a.i./ha]	Retreatment Interval (days)	Total Rate (lb a.i./A) [g a.i./ha]	Surfactant/ Adjuvant
LOWBUSH BLUEBERRIES							
Upper Rawdon, NS/ 2016 (Trial no. 153)	Aprovia Fungicide/ EC (10.3)	1. Foliar broadcast/ Fruiting – 90% blue	27 [251]	0.067 [75]	-	0.135 [151]	Agral 90 (0.2% v/v)
		2. Foliar broadcast/ Fruiting – 95% blue	27 [252]	0.068 [76]	10		
Dean, NS/ 2016 (Trial no. 154)	Aprovia Fungicide/ EC (10.3)	1. Foliar broadcast/ Fruiting – 85% blue	26 [247]	0.066 [74]	-	0.132 [148]	Agral 90 (0.2% v/v)
		2. Foliar broadcast/ Fruiting – 95% blue	26 [246]	0.066 [74]	10		
Milford Field, NS/ 2016 (Trial no. 155)	Aprovia Fungicide/ EC (10.3)	1. Foliar broadcast/ Fruiting - 40% blue	27 [251]	0.067 [75]	-	0.134 [150]	Agral 90 (0.2% v/v)
		2. Foliar broadcast/ Fruiting – 85% blue	27 [249]	0.067 [75]	10		
Caledonia, NS/ 2016 (Trial no. 156)	Aprovia Fungicide/ EC (10.3)	1. Foliar broadcast/ Fruiting – 45% blue	27 [250]	0.067 [75]	-	0.133 [149]	Agral 90 (0.2% v/v)
		2. Foliar broadcast/ Fruiting – 90% blue	26 [247]	0.066 [74]	10		
Mt. Thom, NS/ 2016 (Trial no. 288)	Aprovia Fungicide/ EC (10.3)	1. Foliar broadcast/ BBCH 81 to 89 mixed	29 [272]	0.068 [76]	-	0.137 [153]	Agral 90 (0.2% v/v)
		2. Foliar broadcast/ BBCH 82 to 89 mixed	29 [275]	0.069 [77]	10		
HIGHBUSH BLUEBERRIES							
L'Acadie, QC/ 2016 (Trial no. 157)	Aprovia Fungicide/ EC (10.3)	1. Foliar directed/ Ripening	82 [766]	0.205 [230]	-	0.411 [461]	Agral 90 (0.2% v/v)
		2. Foliar directed/ Mature fruit	82 [771]	0.206 [231]	10		
L'Acadie, QC/ 2016 (Trial no. 158)	Aprovia Fungicide/ EC (10.3)	1. Foliar directed/ Ripening	82 [767]	0.205 [230]	-	0.407 [456]	Agral 90 (0.2% v/v)
		2. Foliar directed/ Mature fruit	81 [754]	0.202 [226]	10		
Jordan Station, ON/ 2016 (Trial no. 159)	Aprovia Fungicide/ EC (10.3)	1. Foliar directed/ Colored fruit	27 [257]	0.069 [77]	-	0.140 [156]	Agral 90 (0.2% v/v)
		2. Foliar directed/ Colored fruit (mature)	28 [264]	0.071 [79]	10		
Langley, BC/ 2016 (Trial no. 160)	Aprovia Fungicide/ EC (10.3)	1. Foliar directed/ 60% mature fruit	31 [287]	0.070 [78]	-	0.140 [156]	Agral 90 (0.2% v/v)
		2. Foliar directed/ 90% mature fruit	31 [287]	0.070 [78]	9		

Blueberries (lowbush and highbush) were grown and maintained according to typical agricultural practices. Irrigation was used at trial sites 157, 158, 159 and 160. No unusual weather conditions were reported to have adversely affected the crop production during the study.

Sample Handling and Preparation

For each trial, two independent samples of mature blueberry were collected from the untreated and treated plots 1 day after the last application. At trial site 157, additional blueberry samples were collected 5, 7, 11 and 14 days after the last application to assess the residue decline behavior. Untreated samples were collected before the treated samples to avoid contamination. Highbush blueberries were harvested by hand and lowbush blueberries were harvested using a hand rake. Samples were collected from a minimum of 12 different areas from each plot

avoiding plot ends. Samples were collected from high and low areas of the plant which contained sheltered and exposed fruit. At trial sites 153, 154, 155 and 156, samples were placed on a clean screen, and a fan was used to remove leaves and stems. All fruit samples weighed greater than the minimum target weight of 1.1 lbs (0.5 kg).

Samples were transported to the test site facility freezer within 6 hours and 25 minutes of collection. All samples were stored frozen at ≤ 0°F (≤ -18°C) until shipment to the analytical laboratory. The study report indicates that the freezer temperature spiked at 21°F (-5.9°C) due to normal variation such as door opening. Samples were shipped frozen to the laboratory via ACDS freezer truck.

All samples arrived frozen and in good condition at Analytical Bio-Chemistry Laboratories, Inc. (Columbia, MO). Upon receipt, samples were stored frozen at ≤ -4°F (≤ -20°C) with temperatures reaching up to 14°F (-10 °C) due to normal variation such as door opening. Blueberry samples were macerated with dry ice using a Robot Coupe food chopper, within 10 days of receipt at the laboratory. Samples were only removed from frozen storage when needed for maceration and extraction.

2. Description of Analytical Procedures

Samples of blueberries (lowbush and highbush) were analyzed for residues of benzovindiflupyr using a working method based on the reference Analytical Method GRM042.03A entitled "SYN545192 – Analytical Method GRM042.03A for the Determination of SYN545192 and its Metabolite SYN546039 in Crops" (PMRA #2255462, EPA #48604405). This method was previously reviewed by the PMRA and deemed adequate for data gathering purposes. Modifications to the method include the use of specific volumes of extraction solvents, more detailed instructions for the remaining steps of the method and used different instrument description and conditions.

Briefly, samples were extracted with acetonitrile:water (80:20) using a homogenizer followed by centrifugation. Aliquots of the extract were diluted with 50:50 acetonitrile:water prior to analysis by high performance liquid chromatography with triple quadrupole mass spectrometer (LC-MS/MS). The LOQ, determined as the lowest level of method validation (LLMV), was set at 0.01 ppm.

The analytical report presented calculated values for the limit of detection (LOD) and LOQ based on recoveries obtained at the 0.01 ppm fortification level. The LOD and LOQ were calculated using the method described in Roy-Keith Smith's Handbook of Environmental Analysis. The calculated LOD and LOQ were 0.00127 ppm and 0.00381 ppm, respectively.

II. RESULTS AND DISCUSSION

Method performance was evaluated during method validation and by use of concurrent recovery samples by fortifying blueberries with benzovindiflupyr at 0.01, 0.02, 0.1, 1.0 and/or 2.0 ppm. All recoveries were within the acceptable range of 70% to 120%; therefore, the method was considered valid for the analysis of benzovindiflupyr residues in blueberry matrices (Table

B.7.6.1.1-4). The fortification levels did bracket the measured residues.

The detector response was linear (coefficient of determination, r^2 >0.994) within the range of 0.02 to 0.2 ng/mL. Representative chromatograms of control samples, fortified samples and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background. The fortified sample chromatograms contained only the analyte of interest, and peaks were symmetrical and well defined.

Table B.7.6.1.1-4. Summary of Procedural/Concurrent Recoveries of Benzovindiflupyr from Blueberries.

Matrix	Fortification Level (ppm)	Recoveries (%)	Mean ± Std. Dev. (%)
Method Validation			
Blueberries	0.01	110, 100, 102, 102, 104, 104	104 ± 3
	0.02	99, 100, 97	99 ± 2
	0.1	101, 103, 105	103 ± 2
	2.0	96, 101, 95	97 ± 3
Concurrent recoveries			
Blueberries	0.01	98	-
	0.1	102, 102, 108, 106	105 ± 3
	1.0	103, 101	102

The field residue samples were stored frozen a maximum of 227 days from harvest to extraction (Table B.7.6.1.1-5). Samples were analyzed within 1 day of extraction.

Freezer storage stability data were previously reviewed and results indicate that residues of benzovindiflupyr were stable when stored frozen at ≤ 0°F (≤ -18 C) in crops from all representative OECD commodity categories (*i.e.* spinach (high water content), orange fruit (high acid content), soybean seed (high oil content), dried broad bean (high protein content) and potato tuber and wheat grain (high starch content)) for up to 24 months (730 – 734 days) (PMRA #2255560 and #2327391, EPA #48604467 and #49120607). Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

Table B.7.6.1.1-5. Summary of Storage Conditions.

Matrix (RAC)	Storage Temperature (°F)/[°C]	Actual Storage Duration (days)[1]	Interval of Demonstrated Storage Stability (days/months)
Blueberries	≤ 0°F [≤ -18°C]	227	Freezer storage stability data were previously reviewed and results demonstrated that residues of benzovindiflupyr were stable when stored frozen for up to 24 months (730-734 days) in crops from all representative OECD commodity categories (high water, high acid, high oil, high starch and high protein) (PMRA #2255560 and #2327391, EPA #48604467 and #49120607).

[1] The interval between harvest and extraction. Samples were analyzed within 1 day of extraction.

The results from the submitted field trials, presented in Tables B.7.6.1.1-6 and B.7.6.1.1-7, showed that average residues of benzovindiflupyr were similar in lowbush and highbush blueberries treated at total seasonal rates ranging from 0.132 to 0.140 lb a.i./A (148 to 156 g a.i./ha).

In lowbush blueberries, individual sample (and per-trial average) residues of benzovindiflupyr were 0.436 ppm to 0.981 ppm (0.475 ppm to 0.866 ppm) following two foliar broadcast applications at a total seasonal rate of 0.132 to 0.137 lb a.i./A (148 to 153 g a.i./ha) and harvested at a PHI of 1 day.

In highbush blueberries, individual sample (and per-trial average) residues of benzovindiflupyr were 0.516 ppm to 1.051 ppm (0.537 ppm to 0.861 ppm) following two foliar directed applications at a total seasonal rate of 0.140 lb a.i./A (156 g a.i./ha) and harvested at a PHI of 1 day. Individual sample (and per-trial average) residues of benzovindiflupyr were 0.337 ppm to 0.551 ppm (0.360 ppm to 0.514 ppm) in highbush blueberries following two foliar directed applications at a total seasonal rate of 0.407 to 0.411 lb a.i./A (456 to 461 g a.i./ha) and harvested at a PHI of 1 day.

In the highbush blueberry residue decline trial, mean residue levels decreased from 0.360 ppm to 0.219 ppm between PHIs of 0 and 11 days and increased slightly to 0.258 ppm at a PHI of 14 days.

Table B.7.6.1.1-6. Residue Data from Blueberries Field Trials with Benzovindiflupyr.

Location: City, Province; Year (Trial ID)	Region	Crop/ Variety	Matrix	End-Use Product	Rate (lb a.i./A) [g a.i./ha]	PHI (days)	Residues (ppm)
LOWBUSH BLUEBERRIES							
Upper Rawdon, NS/ 2016 (Trial no. 153)	1	Lowbush blueberries/ Wild clones	Fruit	Aprovia Fungicide	0.135 [151]	1	0.635, 0.674 [0.655]
Dean, NS/ 2016 (Trial no. 154)	1	Lowbush blueberries/ Wild clones	Fruit	Aprovia Fungicide	0.132 [148]	1	0.701, 0.680 [0.691]
Milford Field, NS/ 2016 (Trial no. 155)	1	Lowbush blueberries/ Wild clones	Fruit	Aprovia Fungicide	0.134 [150]	1	0.514, 0.436 [0.475]
Caledonia, NS/ 2016 (Trial no. 156)	1	Lowbush blueberries/ Wild clones	Fruit	Aprovia Fungicide	0.133 [149]	1	0.510, 0.512 [0.511]
Mt. Thom, NS/ 2016 (Trial no. 288)	1	Lowbush blueberries/ Wild	Fruit	Aprovia Fungicide	0.137 [153]	1	0.751, 0.981 [0.866]
HIGHBUSH BLUEBERRIES							
L'Acadie, QC/ 2016 (Trial no. 157)	5	Highbush blueberries/ Patriot	Fruit	Aprovia Fungicide	0.411 [461]	1	0.382, 0.337 [0.360]
						5	0.332, 0.277 [0.305]
						7	0.255, 0.282 [0.269]
						11	0.246, 0.192 [0.219]
						14	0.227, 0.288 [0.258]
L'Acadie, QC/ 2016 (Trial no. 158)	5	Highbush blueberries/ Norland	Fruit	Aprovia Fungicide	0.407 [456]	1	0.551, 0.476 [0.514]
Jordan Station, ON/ 2016 (Trial no. 159)	5	Highbush blueberries/ Bluecrop	Fruit	Aprovia Fungicide	0.140 [156]	1	0.671, 1.051 [0.861]

Table B.7.6.1.1-6. Residue Data from Blueberries Field Trials with Benzovindiflupyr.							
Location: City, Province; Year (Trial ID)	Region	Crop/ Variety	Matrix	End-Use Product	Rate (lb a.i./A) [g a.i./ha]	PHI (days)	Residues (ppm)
Langley, BC/ 2016 (Trial no. 160)	12	Highbush blueberries/ Liberty	Fruit	Aprovia Fungicide	0.140 [156]	1	0.558, 0.516 [0.537]

Table B.7.6.1.1-7. Summary of Residues from Blueberry Field Trials with Benzovindiflupyr.										
Crop Matrix	Total Application Rate (lb a.i./A) [g a.i./ha]	PHI (days)	n	Residues (ppm)						
				Max.[1]	LAFT[2]	HAFT[2]	Median[2]	Mean[2]	SD[2]
Lowbush blueberries	0.132 – 0.137 [148 – 153]	1	5	0.981	0.475	0.866	0.655	0.640	0.156
Highbush blueberries	0.140 [156]	1	2	1.051	0.537	0.861	0.699	0.699	-
	0.407 – 0.411 [456 – 461]	1	2	0.551	0.360	0.514	0.437	0.437	-

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation

[1] Values based on total number of samples.
[2] Values based on per-trial averages.

III. CONCLUSIONS

The blueberry (lowbush and highbush) field trials are considered scientifically acceptable. The results of the study showed that following a total application of 0.132 to 0.140 lb a.i./A (148 to 156 g a.i./ha) in lowbush and highbush blueberry samples collected at a PHI of 1 day, average benzovindiflupyr residues ranged from 0.475 ppm to 0.866 ppm and 0.537 ppm to 0.861 ppm, respectively. In highbush blueberries treated at a total seasonal rate of 0.407 to 0.411 lb a.i./A (456 to 461 g a.i./ha) and harvested at a PHI of 1 day, average residues of benzovindiflupyr ranged from 0.360 ppm to 0.514 ppm. A decline study indicates that the level of benzovindiflupyr residues in highbush blueberries decreased from PHIs of 0 to 11 days and slightly increased from PHIs of 11 to 14 days. Adequate storage stability data are available to support sample storage durations and conditions.

REFERENCES

PMRA #2255462, EPA #48604405. Braid, S., Lin, K. (2011) SYN545192 – Analytical Method GRM042.03A for the Determination of SYN545192 and its Metabolite SYN546039 in Crops, Report Number: GRM042.03A, Task Number: T001407-08. Unpublished study prepared by Syngenta Crop Protection, LLC, Greensboro, NC, USA, 92p.

PMRA #2255560, EPA #48604467. Watson, G. (2012) SYN545192 - Storage Stability of Residues of SYN545192, SYN546039 and SYN546206 in Crop Matrices Stored Frozen for up to Two Years, 12-Months Storage Stability Report, Report Number: S11-02333-INT3, Task Number: TK0002512. Unpublished study prepared by Syngenta Crop Protection, LLC, Greensboro, NC, USA, 153p.

PMRA #2327391, EPA #49120607. Watson, G. (2013) SYN545192 – Storage Stability of Residues of SYN545192, SYN546039 and SYN546206 in Crop Matrices Stored Frozen for up to Two Years, Final Report. Report Number: S11-02333-REG, Task Number: TK0002512. Unpublished study prepared by Syngenta Crop Protection, LLC, Greensboro, NC, USA, 159 p.

B.7.6 Residues Resulting from Supervised Trials (Annex IIA 6.3; Annex IIIA 8.3)

B.7.6.1 Residues in Target Crops

B.7.6.1.1 Ginseng

Document ID:	MRID No. 50803802 PMRA No. 3051670
Report:	Lennon, G. (2019) Benzovindiflupyr + Difenoconazole: Magnitude of the Residue on Ginseng, IR-4 PR No. 11760, Analytical Laboratory Identification Number 11760.16-MIR12. Unpublished study prepared by IR-4 Project, Rutgers, The State University of New Jersey, Princeton, NJ, USA, 174p.
Guidelines:	EPA OCSPP Harmonized Test Guideline 860.1500 Crop Field Trials (August 1996) PMRA Regulatory Directive DIR98-02 – Residue Chemistry Guidelines, Section 9 – Crop Field Trials PMRA Regulatory Directive DIR2010-05 – Revisions to the Residue Chemistry Crop Field Trial Requirements OECD Guideline 509 Crop Field Trial (September 2009)
GLP Compliance:	No deviations from regulatory requirements were reported which would have an impact on the validity of the study.
Acceptability:	The study is considered scientifically acceptable.
Evaluator:	Natalie Gaudreau, MUAS, HED, PMRA David Nadrchal, EPA

David Nadrchal

EXECUTIVE SUMMARY

Four field trials for benzovindiflupyr and difenoconazole on ginseng were conducted in the United States encompassing North American Free Trade Agreement (NAFTA) Growing Region 5 (4 trials in WI) during the 2016 growing season.

At each trial location, benzovindiflupyr and difenoconazole formulated as Aprovia Top (emulsifiable concentration formulation containing 7.57% benzovindiflupyr and 11.1% difenoconazole) was applied 4 times as a foliar broadcast application at a rate of 0.065 to 0.071 lb a.i./A (73 to 80 g a.i./ha) with retreatment intervals (RTIs) of 13 to 15 days for a total seasonal rate of 0.268 to 0.278 lb a.i./A (300 to 311 g a.i./ha). An adjuvant, Scanner, was added to the spray mixture for all applications at a rate of 0.03% (v/v). Fresh ginseng roots were harvested at a preharvest interval (PHI) of 15 days. In one trial, samples were collected at different time intervals (PHIs of 0, 2, 8 and 21 days) to monitor residue decline. The fresh ginseng roots were dried in a dryer to commercial/protocol standard (70-90% dry matter) before sample collection.

All samples were maintained frozen at the testing facility, during shipping to the laboratory, and were stored frozen until analysis. The maximum storage interval for samples between harvest

and extraction was 460 days (~ 15 months). Samples were analyzed within 4 days of extraction. Residues of benzovindiflupyr and metabolite SYN546039 have been shown to be stable in crops from all representative OECD commodity categories (*i.e.* spinach (high water content), orange fruit (high acid content), soybean seed (high oil content), dried broad bean (high protein content) and potato tuber and wheat grain (high starch content)) for up to 730-734 days under frozen conditions. Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

Samples in the current study were analyzed using a working method based on the reference Method GRM042.03A, a LC-MS/MS method to determine residues of benzovindiflupyr and metabolite SYN546039. The study report indicated that samples were not analyzed for residues of difenoconazole as difenoconazole is currently registered for use on ginseng. Acceptable method validation and concurrent recoveries were reported for benzovindiflupyr and metabolite SYN546039 on dried ginseng root samples at fortification levels of 0.01, 0.1 and/or 1.0 mg/kg (ppm), thus validating the method. The limit of quantitation (LOQ) was 0.01 ppm per analyte for dried ginseng roots.

Individual sample (and per-trial average) residues of benzovindiflupyr in dried ginseng roots ranged from 0.0326 ppm to 0.161 ppm (0.0336 ppm to 0.145 ppm) following 4 broadcast applications at total seasonal rates of 0.268 to 0.278 lb a.i./A (300 to 311 g a.i./ha) and harvested at a PHI of 15 days. Residues of the metabolite SYN546039 were all below LOQ (<0.01 ppm).

In the residue decline trial, mean residue levels of benzovindiflupyr decreased from 0.0511 ppm to 0.0302 ppm in dried ginseng roots between PHIs of 0 and 8 days and increased up to 0.0677 ppm at a PHI of 21 days. Residues of metabolite SYN546039 in dried ginseng roots were all below LOQ (<0.01 ppm) at all time points, therefore, residue decline could not be assessed.

I. MATERIALS AND METHODS

A. MATERIALS

Table B.7.6.1.1-1. Nomenclature for Benzovindiflupyr and Metabolites of Interest.	
Common name	Benzovinflupyr
Identity	*N*-[9-(dichloromethylene)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-5-yl]-3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxamide
CAS no.	1072957-71-1
Company experimental name	SYN545192
Metabolite	SYN546039
Identity	3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxylic acid ((1S,2R,4R)-9-dichloromethylene-2-hydroxy-1,2,3,4-tetrahydro-1,4-methano-naphthalen-5-yl)-amide

B. Study Design

1. Test Procedure

A total of 4 residue trials in/on ginseng were conducted with an emulsifiable concentrate formulation during the 2016 growing season (Table B.7.6.1.1-2).

Table B.7.6.1.1-2. Trial Numbers and Geographical Locations.															
Crop	Region														Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Ginseng	-	-	-	-	4	-	-	-	-	-	-	-	-	-	4

All trials, except for those listed in the table below, were separated by ≥ 20 miles (≥ 32 km) and are therefore considered independent (568_Criteria for Independence of Trials, November 2014). The trials separated by < 20 miles (< 32 km) have been assessed for independence as detailed in the table below. HED has determined that there are sufficient differences between the trials that they may be considered separate.

Independent Trial Determination[1]		
Trial Nos.	Differences	Decision
16-MI215 and 16-MI216	Location: Wausau, WI and Mosinee, WI Variety: American (both sites) Timing: 1st applications were made the same day. Spray mixture: an independent spray mixture was prepared for each trial site. Crop maturity: 4 years old (Trial 16-MI215) and 5 years old (Trial 16-MI216)	Separate due to different crop maturity and an independent spray mixture was used.

[1] All assessments are based on the replicate trial guidance presented in memorandum Criteria for Independence of Crop Field Trials, November 2014.

Locations and detailed use patterns for the trials are provided in Table B.7.6.1.1-3.

Table B.7.6.1.1-3. Study Use Pattern.

Location: City, State; Year (Trial ID)	End-use Product/ Formulation[1]	Method of Application/ Timing of Application	Volume (gal/A) [L/ha]	Rate per Application (lb a.i./A) [g a.i./ha]	Retreatment Interval (days)	Total Rate (lb a.i./A) [g a.i./ha]	Surfactant/ Adjuvant
Hatley, WI/ 2016 (Trial no. 16-MI182)	Aprovia Top/ EC	1. Foliar broadcast/ Fruiting	69	0.068 [76]	-	0.275 [307]	Scanner (0.03% v/v)
		2. Foliar broadcast/ Fruiting	70	0.069 [77]	15		
		3. Foliar broadcast/ Fruiting	71	0.069 [77]	13		
		4. Foliar broadcast/ Fruiting	71	0.069 [77]	13		
Athens, WI/ 2016 (Trial no. 16-MI214)	Aprovia Top/ EC	1. Foliar broadcast/ Vegetative	72	0.071 [80]	-	0.278 [311]	Scanner (0.03% v/v)
		2. Foliar broadcast/ Flowering	71	0.069 [77]	15		
		3. Foliar broadcast/ Fruiting	71	0.070 [78]	14		
		4. Foliar broadcast/ Fruiting	69	0.068 [76]	13		
Wausau, WI/ 2016 (Trial no. 16-MI215)	Aprovia Top/ EC	1. Foliar broadcast/ Vegetative	69	0.068 [76]	-	0.272 [305]	Scanner (0.03% v/v)
		2. Foliar broadcast/ Fruiting	73	0.071 [80]	15		
		3. Foliar broadcast/ Fruiting	67	0.065 [73]	13		
		4. Foliar broadcast/ Fruiting	70	0.068 [76]	13		
Mosinee, WI/ 2016 (Trial no. 16-MI216)	Aprovia Top/ EC	1. Foliar broadcast/ Vegetative	67	0.066 [74]	-	0.268 [300]	Scanner (0.03% v/v)
		2. Foliar broadcast/ Fruiting	68	0.067 [75]	15		
		3. Foliar broadcast/ Fruiting	68	0.067 [75]	13		
		4. Foliar broadcast/ Fruiting	69	0.068 [76]	13		

[1] The end-use product, Aprovia Top, contains 7.57% benzovindiflupyr and 11.1% difenoconazole.

Ginseng were grown and maintained according to typical agricultural practices. Irrigation was not used at any trial site. No unusual weather conditions were reported to have adversely affected the crop production during the study.

Sample Handling and Preparation

For each trial, two independent samples of ginseng were collected from the untreated and treated plots 15 days after the last application. At trial site 16-WI216, additional ginseng samples were collected 0, 2, 8 and 21 days after the last application to assess the residue decline behavior. Untreated samples were collected before treated samples to avoid contamination. Fresh ginseng roots were collected from 12 areas of the plot avoiding plot ends. Fresh ginseng roots were harvested using potato forks to loosen the soil around the roots after which they were handpicked and placed into bags. The roots were hand washed by softly agitating the roots in the water until the majority of the dirt was removed. The roots were not scrubbed. After washing, the roots were spread onto drying racks and placed into dryers. Separate dryers were used for untreated and treated samples. The fresh ginseng roots were dried to commercial/protocol standards, an

estimated 70-90% dry matter. After drying was complete, the roots were collected by hand and placed in sample bags into coolers containing dry ice for shipping to the testing facility. All dried ginseng root samples weighed greater than the minimum target weight of 2 lbs (0.9 kg).

Samples were stored frozen < 0°F (-18°C) within 10 minutes of collection. All samples were shipped frozen to the analytical laboratory via FedEx. Samples arrived frozen and in good condition at the IR-4 North Central Region Laboratory at Michigan State University (Lansing, MI). Upon receipt, samples were stored frozen at < -4°F (< -20°C) until processed. The roots were ground using a Robot Coupe RS1 10B with dry ice. Untreated samples were chopped first followed by treated samples. The entire sample was chopped and homogenized. Chopped samples were placed in labeled glass jars and stored frozen until analysis.

2. Description of Analytical Procedures

Samples of dried ginseng roots were analyzed for residues of benzovindiflupyr and metabolite SYN546039 using a working method based on the reference Analytical Method GRM042.03A entitled "SYN545192 - Analytical Method GRM042.03A for the Determination of SYN545192 and its Metabolite SYN546039 in Crops" (PMRA #2255462, EPA #48604405). This method was previously reviewed by the PMRA and deemed adequate for data gathering purposes. Modifications to the method include partitioning the extract 4 times with isohexane instead of 3 times using smaller volumes, an Agilent Bond Elut PH SPE column was used instead of a Waters Oasis HLB-SPE column to improve cleanup, additional cleanup was required for the metabolite analysis and matrix matched standards were used for metabolite SYN546039 to generate the calibration curve to minimize matrix effects. The study report indicated that residues of difenoconazole were not analyzed since this active ingredient is registered for use on ginseng.

Briefly, samples were extracted with acetonitrile:water (80:20) using a homogenizer followed by centrifugation. An aliquots of the extract was evaporated to remove the acetonitrile and 1 M HCl was added. The acidified aliquot was partitioned 4 times with isohexane and both the isohexane and the acidified portions were retained. The isohexane portion was concentrated to dryness and acetonitrile:water (50:50, v:v) was added. This fraction was analyzed by HPLC-MS/MS using multiple reaction monitoring (MRM) for benzovindiflupyr.

The acidific aqueous portion of the aliquot was transferred into a glass centrifuge tube and heated at 100°C for 6 hours in a water bath with agitation to hydrolyze conjugates of SYN546039. The sample extract was cooled then spiked with SYN546039. The hydrolysate was cleaned up on an Agilent Bond Elute – phenyl modified (PH) SPE column. The eluate was collected into centrifuge tubes containing 3-aminopropyl functionalized silica gel (PSA) for additional cleanup. Samples were diluted with acetonitrile:water (50:50, v:v) as required prior to analysis by HPLC-MS/MS using multiple reaction monitoring (MRM) and matrix matched standards for SYN546039. The LOQ, determined as the lowest level of method validation (LLMV), was set at 0.01 ppm for benzovindiflupyr and metabolite SYN546039.

The analytical report indicated that extensive method development for the analysis of the metabolite SYN546039 prior to the method validation was required to improve recoveries from ginseng at the lowest level of method validation (LLMV) of 0.01 ppm. The use of the original

HLB SPE column from the reference method was not successful. The use of the PH-SPE column resulted in a cleaner fraction. The PSA step was also added for additional cleanup. Since ginseng is a difficult matrix and there was still significant matrix suppression, matrix matched standards were used to generate consistent results for the metabolite.

II. RESULTS AND DISCUSSION

Method performance was evaluated during method validation and by use of concurrent recovery samples by fortifying dried ginseng roots with benzovindiflupyr at 0.01 ppm, 0.1 ppm and/or 1.0 ppm and with metabolite SYN546039 at 0.01 ppm and/or 0.1 ppm. Recoveries of benzovindiflupyr were generally within the acceptable range of 70-120%; however, low recoveries were observed at all spiking levels. Recoveries of the metabolite SYN546039 were generally within the acceptable range of 70-120% with the exception of the 0.01 ppm spiking level, low recoveries were observed. According to the study report, these low recoveries were acceptable since the standard deviations were less than 10% for both benzovindiflupyr and metabolite SYN546039. Furthermore, similar recoveries were observed whether as a concurrent or method validation recovery. Therefore, the method was considered valid for the analysis of benzovindiflupyr and metabolite SYN546039 residues in dried ginseng root matrices (Table B.7.6.1.1-4).

The detector response was linear (coefficient of determination, $r^2 > 0.982$ for benzovinflupyr and $r^2 > 0.987$ for SYN546039) within the range of 0.00008 to 0.008 µg/mL for both analytes. Representative chromatograms of control samples, fortified samples and treated samples were provided. The control chromatograms generally had no peaks of interest above the chromatographic background. The fortified sample chromatograms contained only the analyte of interest, and peaks were symmetrical and well defined. Residues of metabolite SYN546039 were not expressed in parent equivalents since these were all below LOQ.

Table B.7.6.1.1-4. Summary of Procedural/Concurrent Recoveries of Benzovindiflupyr from Dried ginseng roots.

Matrix	Analyte	Fortification Level (ppm)	Recoveries (%)	Mean ± Std. Dev. (%)
Method Validation				
Dried ginseng roots	Benzovindiflupyr	0.01	66, 74, 72	71 ± 4
		0.1	62, 64, 71	66 ± 5
		1.0	69, 77, 82	76 ± 7
	Metabolite SYN546039	0.01	65, 74, 72	70 ± 5
		0.1	115, 112, 110	112 ± 3
Concurrent Recoveries[1]				
Dried ginseng roots	Benzovindiflupyr	0.01	78, 74, 63	72 ± 8
		0.1	86	-
	Metabolite SYN546039	0.01	71*, 65, 67, 70	68 ± 3

[1] All concurrent recovery samples were analyzed twice and the values reported are averages of multiple analysis.
* Average of 3 injections.

The field residue samples were stored frozen a maximum of 460 days from harvest to extraction (Table B.7.6.1.1-5). Samples were analyzed within 4 days of extraction.

Freezer storage stability data were previously reviewed and results indicate that residues of benzovindiflupyr and metabolite SYN546039 were stable when stored frozen at ≤ 0°F (≤ -18 C)

in crops from all representative OECD commodity categories (*i.e.* spinach (high water content), orange fruit (high acid content), soybean seed (high oil content), dried broad bean (high protein content) and potato tuber and wheat grain (high starch content)) for up to 24 months (730 – 734 days) (PMRA #2255560 and #2327391, EPA #48604467 and #49120607). Adequate storage stability data are therefore available to support the storage conditions and intervals for samples in the current trials.

Table B.7.6.1.1-5. Summary of Storage Conditions.

Matrix (RAC)	Storage Temperature (°F)/[°C]	Actual Storage Duration (days)[1]	Interval of Demonstrated Storage Stability (days/months)
Dried ginseng roots	≤ 0°F [≤ -18°C]	460	Freezer storage stability data were previously reviewed and results demonstrated that residues of benzovindiflupyr and metabolite SYN546039 were stable when stored frozen for up to 24 months (730-734 days) in crops from all representative OECD commodity categories (high water, high acid, high oil, high starch and high protein) (PMRA #2255560 and #2327391, EPA #48604467 and #49120607).

[1] The interval between harvest and extraction. Samples were analyzed within 4 days of extraction.

The results from these trials showed that when harvested 15 days after the last of 4 foliar broadcast applications at total seasonal rates of 0.268 to 0.278 lb a.i./A (300 to 311 g a.i./ha), average residues of benzovindiflupyr in dried ginseng roots ranged from 0.0336 ppm to 0.145 ppm and residues of metabolite SYN546039 were all below LOQ (<0.01 ppm) (Tables B.7.6.1.1-6 and B.7.6.1.1-7). Combined average residues of benzovindiflupyr and metabolite SYN546039 ranged from <0.0436 ppm to <0.155 ppm.

In the residue decline trial, mean residue levels of benzovindiflupyr decreased from 0.0511 ppm to 0.0302 ppm in dried ginseng roots between PHIs of 0 and 8 days and increased up to 0.0677 ppm at a PHI of 21 days. Residues of metabolite SYN546039 in dried ginseng roots were all below LOQ (<0.01 ppm) at all time points, therefore, residue decline could not be assessed.

Table B.7.6.1.1-6. Residue Data from Ginseng Field Trials with Benzovindiflupyr.

Location: City, State; Year (Trial ID)	Region	Crop/ Variety	Matrix	End-Use Product[1]	Rate (lb a.i./A) [g a.i./ha]	PHI (days)	Residues[1] (ppm) [Average]		
							Benzovindiflupyr	Metabolite SYN546039[3]	Total[2,3]
Hatley, WI/ 2016 (Trial no. 16-MI182)	5	Ginseng/ American	Dried roots	Aprovia Top/ EC	0.275 [307]	15	0.0954, 0.0935 [0.0945]	<0.01, <0.01 [<0.01]	<0.1054, <0.1035 [<0.1045]
Athens, WI/ 2016 (Trial no. 16-MI214)	5	Ginseng/ American	Dried roots	Aprovia Top/ EC	0.278 [311]	15	0.0345, 0.0326 [0.0336]	<0.01, <0.01 [<0.01]	<0.0445, <0.0426 [<0.0436]
Wausau, WI/ 2016 (Trial no. 16-MI215)	5	Ginseng/ American	Dried roots	Aprovia Top/ EC	0.272 [305]	15	0.129, 0.161 [0.145]	<0.01, <0.01 [<0.01]	<0.139, <0.171 [<0.155]

Table B.7.6.1.1-6. Residue Data from Ginseng Field Trials with Benzovindiflupyr.

Location: City, State; Year (Trial ID)	Region	Crop/ Variety	Matrix	End-Use Product[1]	Rate (lb a.i./A) [g a.i./ha]	PHI (days)	Residues[1] (ppm) [Average]		
							Benzovindiflupyr	Metabolite SYN546039[3]	Total[2,3]
Mosinee, WI/ 2016 (Trial no. 16-MI216)	5	Ginseng/ American	Dried roots	Aprovia Top/ EC	0.268 [300]	0	0.0491, 0.0530 [0.0511]	<0.01, <0.01 [<0.01]	<0.0591, <0.0630 [<0.0611]
						2	0.0464, 0.0480 [0.0472]	<0.01, <0.01 [<0.01]	<0.0564, <0.0580 [<0.0572]
						8	0.0331, 0.0273 [0.0302]	<0.01, <0.01 [<0.01]	<0.0431, <0.0373 [<0.0402]
						15	0.0564, 0.0563 [0.0564]	<0.01, <0.01 [<0.01]	<0.0664, <0.0663 [<0.0664]
						21	0.0677, 0.0676 [0.0677]	<0.01, <0.01 [<0.01]	<0.0777, <0.0776 [<0.0777]

[1] The end-use product, Aprovia Top, contains 7.57% benzovindiflupyr and 11.1% difenoconazole.
[2] Total = Parent + Metabolite SYN546039
[3] Residues of metabolite SYN5460139 were not expressed as parent equivalents since these were below LOQ (<0.01 ppm).

Table B.7.6.1.1-7. Summary of Residues from Ginseng Field Trials with Benzovindiflupyr.

Crop Matrix	Analyte	Total Application Rate (lb a.i./A) [g a.i./ha]	PHI (days)	n	Residues (ppm)					
					Max.[2]	LAFT[3]	HAFT[3]	Median[3]	Mean[3]	SD[3]
Dried ginseng roots	Benzovindiflupyr	0.268 – 0.278 [300 – 311]	15	4	0.161	0.0336	0.145	0.0755	0.0824	0.0487
	SYN546039[1]				<0.01	<0.01	<0.01	<0.01	<0.01	-
	Combined residues				<0.171	<0.0436	<0.155	0.0855	0.0924	0.0487

n = number of independent field trials, LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation

[1] Residues of metabolite SYN5460139 were not expressed as parent equivalents since these were below LOQ (<0.01 ppm).
[2] Values based on total number of samples.
[3] Values based on per-trial averages.

Note 1: For computation of the LAFT, HAFT, median, mean, and standard deviation, values < LOQ are assumed to be at the LOQ (0.01 ppm).

III. CONCLUSIONS

The ginseng field trials are considered scientifically acceptable. The results of the study showed that following a total application of 0.268 to 0.278 lb a.i./A (300 to 311 g a.i./ha) in ginseng samples collected at PHIs of 15 days, individual sample (and per-trial average) residues of benzovindiflupyr ranged from 0.0326 ppm to 0.161 ppm (0.0336 ppm to 0.145 ppm) and residues of metabolite SYN546039 were all below LOQ (<0.01 ppm).

In the residue decline trial, mean residue levels of benzovindiflupyr decreased from 0.0511 ppm to 0.0302 ppm in dried ginseng roots between PHIs of 0 and 8 days and increased up to 0.0677 ppm at a PHI of 21 days. Residues of metabolite SYN546039 in dried ginseng roots were all below LOQ (<0.01 ppm) at all time points, therefore, residue decline could not be assessed.

An acceptable method was used for residue quantitation and adequate storage stability data are available to support sample storage durations and conditions for benzovindiflupyr and metabolite SYN546039.

REFERENCES

PMRA #2255462, EPA #48604405. Braid, S., Lin, K. (2011) SYN545192 – Analytical Method GRM042.03A for the Determination of SYN545192 and its Metabolite SYN546039 in Crops, Report Number: GRM042.03A, Task Number: T001407-08. Unpublished study prepared by Syngenta Crop Protection, LLC, Greensboro, NC, USA, 92p.

PMRA #2255560, EPA #48604467. Watson, G. (2012) SYN545192 - Storage Stability of Residues of SYN545192, SYN546039 and SYN546206 in Crop Matrices Stored Frozen for up to Two Years, 12-Months Storage Stability Report, Report Number: S11-02333-INT3, Task Number: TK0002512. Unpublished study prepared by Syngenta Crop Protection, LLC, Greensboro, NC, USA, 153p.

PMRA #2327391, EPA #49120607. Watson, G. (2013) SYN545192 – Storage Stability of Residues of SYN545192, SYN546039 and SYN546206 in Crop Matrices Stored Frozen for up to Two Years, Final Report. Report Number: S11-02333-REG, Task Number: TK0002512. Unpublished study prepared by Syngenta Crop Protection, LLC, Greensboro, NC, USA, 159 p.